UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,460	10/16/2001	Daniel S. Kohane	0492611-0418 (MIT 9023)	5906

24280 7590 11/14/2006

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,460	KOHANE ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-48,60,61,63,65-76 and 79* is/are pending in the application.

4a) Of the above claim(s) *25,28,34-36 and 41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-24,26,27,29-33,37-40,45-48,60,61,63, 65-76 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment filed 8/28/2006 is acknowledged. After entry of the amendment, claims 1, 2, 7-48, 60, 61, 63, 65-76 and 79 are pending. Claims 25, 28, 34-36 and 41-44 remain withdrawn as directed to non-elected species. Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-48, 60, 61, 63, 65-76 and 79 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7-24, 26, 27, 29-33, 37-40, 45-48, 60, 61, 63 and 65-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by amendment of the claims.**

Claims 1, 63, 65, 69, and 73 (from which all other rejected claims depend) have been amended (e.g. in line 7 of claim 1) to recite microparticles comprising a polynucleotide encapsulated in a matrix wherein the microparticles "are not hollow." The "not hollow" limitation introduces confusion into the claims because the polynucleotide is recited as encapsulated in the matrix, thus implying the microparticles surround the polynucleotide as a capsule. It is therefore unclear how the "not hollow" limitation further limits the claimed microparticles. Does it mean all of the polynucleotides are completely within the matrix? The specification does not mention the word "hollow" and thus provides no guidance on how this limitation is to limit the claimed subject matter, or how it is to be interpreted. This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-48, 60, 61, 63 and 65-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by amendment of the claims. This is a New Matter rejection.**

Amended claims 1, 63, 65, 69, and 73 recite a matrix comprising "20-60% by weight lipid", "10-30% by weight protein", "10-30% by weight sugar", microparticles that "are not hollow", "wherein the lipid, protein and sugar of the matrix are not part of substantially cross-linked particles", and wherein the microparticles range "from 0.5-10 micrometers in diameter." Amended claims 2 recites microparticles comprising a matrix that may comprise "20-60% lipid by weight", "10-30% protein by weight", or "10-30% sugar by weight", and wherein the microparticles range "from 0.5-10 micrometers in diameter." The response indicates support for the amendments may be found in the specification at page 3, lines 4-5, page 25, lines 10-13, in the "Methods of Making Microparticles" section, Figure 1, and original claims 51, 53, 57, 59 and 62. These passages do not recite microparticles that "are not hollow" or wherein the matrix is not part of "substantially cross-linked particles." The remainder of the specification does not recite these limitations. Figure 1 depicts micrographs of a single example of the claimed

microparticles, but it cannot be determined if they are hollow. That is, absent evidence to the contrary, an electron microscope cannot visualize the interior of a structure, only the surface (see ¶ [0094] of the publication of the instant application, US 20020150626 A1). In fact, it could be argued that the microparticles in Fig. 1 are "hollow", as they appear to be doughnut-like ring structures with a hollow space in the center. Therefore, there is no support for the limitations wherein the microparticles "are not hollow" or wherein the lipid, protein and sugar of the matrix are not part of "substantially cross-linked particles." Furthermore, there is no evidence that applicant's considered such limitations as part of their invention. Thus, the amended claims include impermissible New Matter.

Regarding the limitations of percent weight and the diameter of the microparticles, the only disclosure of the 20-60% by weight lipid, 10-30% by weight protein and 10-30% by weight sugar limitations was in original claims 51, 53, and 57 (all dependent from original claim 1), respectively. Although there is no specific disclosure of a range of microparticle diameters from 0.5-10 micrometers (μm), original claims 59 and 62 (both dependent from original claim 1) recite diameters of less than 10 or 0.5 micrometers, respectively. Thus, the range of from 0.5-10 μm is derived from excluding the genus of original claim 62 (0.5 μm or less) from that of original claim 59 (less than 10 μm or less). Original claim 1 discloses an extremely broad genus of compositions "comprising microparticles of a polynucleotide encapsulated in a matrix comprising lipid, protein, and sugar." All of the above dependent claims introduce their respective limitations individually, not in conjunction. Thus, there is no support for the subgenus as instantly claimed wherein all three of the weight percent limitations are combined with a microparticle size limitation. There is no evidence that applicant's considered the claimed

subgenus of compositions as there invention. Thus, the amended claims include impermissible New Matter.

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Applicants assert (on pages 18-19 of the response) that the limitation "wherein the lipid, protein and sugar of the matrix are not part of substantially cross-linked particles" is not New Matter because the facts of the instant case are addressed in the *In re Johnson* decision. This is not convincing because in order to exclude a species, the species must first be disclosed. There are no teachings in the instant application of a species wherein cross-linking is not substantial, nor even mention of cross-linking. Thus, applicants cannot exclude this species. Furthermore, it is doubtful applicants microspheres are "not cross-linked." This is because some forces/bonds are holding the components of the microspheres together, e.g. covalent bonding or Van der Waals forces, thus the components of the microspheres are cross-linked.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 7-17, 20-24, 26, 27, 29-33, 37-38, 40, 45-47, 60, 61, 65-70, 73-74, and 79 under 35 U.S.C. 102(b) as anticipated by Sutton is withdrawn in light of the limitation that the claimed microparticles comprise 10-30% by weight protein. This limitation is not taught by Sutton.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7-17, 20-24, 26, 27, 29-33, 37-38, 40, 45-47, 60, 61, 65-70, 73-74, and 79 are rejected under 35 U.S.C. 103(a) as obvious over Sutton (6,204,054). **This rejection is maintained for reasons made of record in previous Office Actions (6/15/04, 1/11/2005, and 2/24/2006) and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Applicants repeat many of the arguments set forth in previous responses, which have already been addressed in the Office Actions above. To the extent that applicant's arguments are novel, and directed to an obviousness rejection, they are summarized below. Applicants essentially assert that: 1) Sutton uses lactose as a carrier or excipient, added after the microparticle is formed, and thus lactose is not a component of the matrix or microparticle; 2)

Sutton does not teach microparticles with "10-30% by weight protein", but rather teaches away from this weight range by disclosing that the microparticles comprise "at least 50% by weight transcytosis enhancer"; 3) Sutton teaches "hollow particles" prepared by spray drying whereas the microparticles of the instant invention are "not hollow."

Regarding 1), the addition of lactose as an excipient is considered an addition to the "matrix" of the microparticles taught by Sutton. This is because of a lack of a definition for "matrix" in the instant specification, hence the term is interpreted, in order to be consistent with usage of the term in the art, as follows:

1. A surrounding substance within which something else originates, develops, or is contained. From *The American Heritage Stedman's Medical Dictionary, 2002.*

Thus, the matrix comprises the materials used to contain, or encapsulate, the polynucleotide of the instant claims. Lactose, as disclosed by Sutton, is considered to be such a material, regardless of when it is added to the microparticles of Sutton because it is used to "contain" or encapsulate any polynucleotides within the microparticles taught by Sutton. Furthermore, Sutton discloses that the "microparticles may be formulated with ...lactose" (column 9, lines 10-12), implying formation of microparticles with lactose. Regarding 2), the cited passage of Sutton does not teach away from the instant weight percent of protein, but rather indicates that the transcytosis vesicles of the invention may "comprise at least 50% ...by weight transcytosis enhancer." There are no teachings in Sutton that a lesser weight percentage of protein is undesirable, or that the transcytosis vesicles must have at least 50% by weight protein. Furthermore, the obviousness of ranges that do not overlap, but are close enough that one of skill

in the art would have expected the same properties, is considered *prima facie* obvious. See MPEP 2144.05, which also states: "*Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.*" Applicants demonstrate no critical or unexpected results from using the claimed weight percent of protein.

Regarding 3), there is no evidence that applicant's microparticles are not hollow, see the explanation in the New Matter rejection above. Furthermore, it is noted that applicants and Sutton prepare microparticles by spray-drying, and applicants cited Sutton as a source of methods for spray drying (¶ [0077] of US 20020150626 A1). Absent evidence to the contrary, the use of the same method to prepare microparticles results in microparticles of the same structure, i.e. hollow or not hollow.

Thus, the Sutton reference a renders the claimed invention as a whole *prima facie* obvious.

Claims 1, 18, 19, and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutton (as above) taken with Grinstaff (5,639,473).

Claims 69, 71, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutton (as above) taken with Wheeler (5,976,567).

It is noted that an inadvertent error in the Office Action of 2/24/2006 identified the Grinstaff reference regarding a maintained 103(a) rejection of claims 69, 71 and 72 together with Sutton. Rather, the rejection being maintained, from the Office Action of 1/11/2005, was Sutton taken with Wheeler (5,976,567). Thus, it is not new grounds of rejection. **These rejections are**

maintained for reasons made of record in previous Office Actions (6/15/04, 1/11/2005, and 2/24/2006) and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Many of applicant's arguments for this 103(a) rejection are essentially the same arguments as addressed above in the Sutton 103 (a) rejection and thus are addressed as above. To the extent that applicant's arguments are novel, have not been addressed in a previous Office Action, and are directed to an obviousness rejection, they are summarized below. Applicants essentially assert that: 1) Sutton and Grinstaff are mere laundry lists of various agents that might be included in the disclosed microparticles and as such are not enabling; 2) Sutton and Grinstaff do not teach the claimed weight ranges; 3) the microparticles of Grinstaff are cross-linked, as opposed to applicant's particles, which are not cross-linked; 4) the microparticles of Grinstaff are modified by covalently bonding lipids, proteins and sugars to the polymeric shell, and thus are not components of the matrix; 5) there is no teaching to combine the Sutton and Grinstaff references because they are mutually exclusive, because Grinstaff teaches encapsulation of the biologics in the polymeric shell (i.e. not hollow), whereas Sutton teaches hollow microparticles.

Regarding 1), techniques to make the compositions taught by Sutton and Grinstaff were clearly routine in the art, because both references made the disclosed compositions, hence both references are enabled. Applicants present no evidence as to why one of skill in the art could not make the compositions as taught by Sutton and Grinstaff. See MPEP 2121, in particular 2121.02. It is noted that such evidence would also indicate applicant's invention is not enabled because the methods of Sutton are also used in the instant application. Regarding 2), see the

related arguments and response in the above USC 103(a) rejection over Sutton. Regarding 3), there are no teachings in the instant invention of "cross-linking", hence the claims reciting this limitation are New Matter. Furthermore, applicants microparticles are cross linked in some manner, either through covalent bonds or Van der Waals forces, otherwise the microparticles would not form. Regarding 4), any covalent bonding of additional components to the shells of Grinstaff constitutes an addition to the "matrix", as explained above in the response to the Sutton USC 103(a) rejection. Regarding 5), the references are clearly analogous art and the motive to combine the references has been previously established. That Sutton and Grinstaff teach different microparticles is not relevant, nor is it clear what applicant believes is mutually exclusive of these different particles. Grinstaff is only relied upon to provide prior art teachings of the use of microparticles for delivering DNA encoding viral or bacterial antigens as in a vaccine.

Claims 1, 2, 7-24, 26, 27, 29-31, 33, 37-40, 45-48, 60-63, 65-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes (5,855,913). **This rejection is maintained for reasons made of record in previous Office Actions (6/15/04, 1/11/2005, and 2/24/2006) and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Many of applicant's arguments for this 103(a) rejection are essentially the same arguments as addressed in the above 103(a) rejections, and thus are addressed as above. To the extent that applicant's arguments are novel and have not been addressed in a previous Office

Action, they are summarized below. Applicants essentially assert that Hanes cannot render obvious the microparticles of the claimed invention because Hanes teaches that particles of a diameter less than 5 μm deliver agents less effectively, rendering the results obtained with the instantly claimed microparticles (which are less than 5 μm in diameter) unexpected and unobvious. In response, the only particles taught by the instant specification that can be construed to meet the instant claim limitations is the LPSP particle in Table 1 (and probably Table 2, as the specification is unclear as to the weight % of the Table 2 particle) with 60% DPPC loaded with Bupivacaine (thus not encapsulating a polynucleotide). The diameter of this particle was 4.44 +/- 0.39 μm, i.e. very close to the particle diameter of Hanes, and thus does not provide any unexpected properties in relation to the Hanes particles. This is presuming the same results would be found for a microparticle encapsulating a polynucleotide, as instantly claimed. Furthermore, the instant claims encompass many of the embodiments disclosed by Hanes, i.e. microparticles with diameters of from 5-10 μm.

Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-48, 60-63, 65-69, and 73-76, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes taken with any of Grinstaff, Sutton, or Rypacek (GB 2174097 A), and further in view of Wheeler (5,976,567). **This rejection is maintained for reasons made of record in previous Office Actions (6/15/04, 1/11/2005, and 2/24/2006) and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Many of applicant's arguments for this 103(a) rejection are essentially the same

arguments as addressed in the above 103(a) rejections, and thus are addressed as above. To the extent that applicant's arguments are novel and have not been addressed in a previous Office Action, they are summarized below. Applicants argue the Hanes and Wheeler references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants assert that Rypacek teach cross-linked particles, which are not a feature of the instant invention. In response, this issue has already been addressed, see the Sutton 103(a) rejection and the New Matter rejection above. Applicants assert that the combined references do not teach the size limitation of the instant invention, and that Hanes teaches away from particles larger than 5 μm. In response, this issue regarding Hanes has already been addressed, see the Hanes USC 103(a) rejection above. Furthermore, Sutton teaches microparticles within the claimed range (2-5 um, claim 14) and thus anticipates this range. Wheeler was not relied upon for a particle diameter, thus arguments that Wheeler teaches away from using particles larger than 0.15 μm are not persuasive.

Finally, applicants assert that the Examiner has relied upon hindsight reasoning in constructing a case for obviousness. In response, clear motivations and suggestions to modify the above references have been supplied in each USC 103(a) rejection. See the Office Actions of 6/15/04, 1/11/05, and 2/24/06.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER